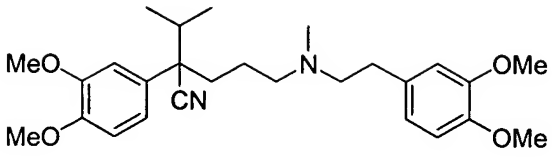
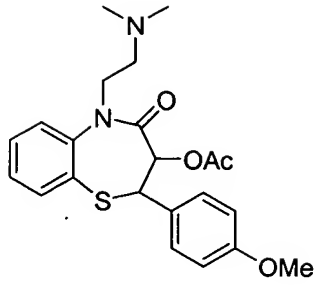
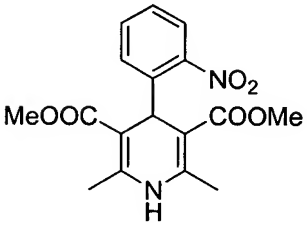


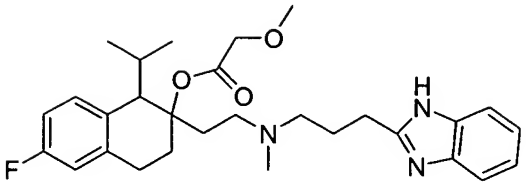
Verapamil



Diltiazem

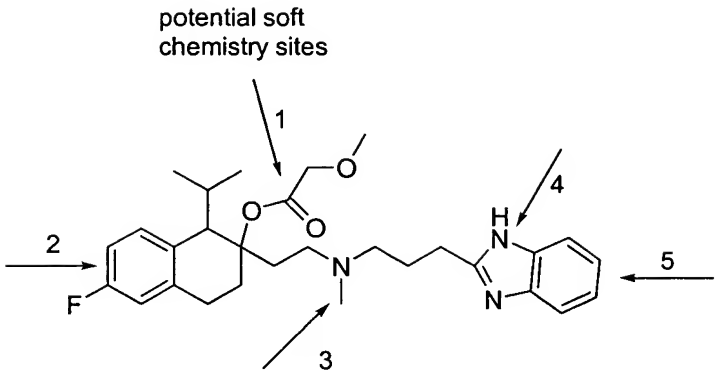


Nifedipine



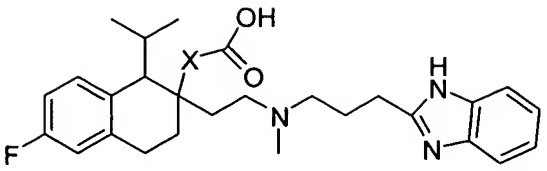
Mibefradil

Figure 1



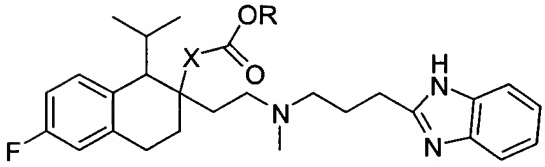
Mibefradil

Figure 2



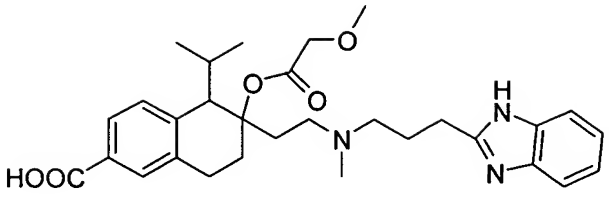
primary inactive metabolite
X = bond, CH_2, or OCH_2

Hydrolytic enzymes

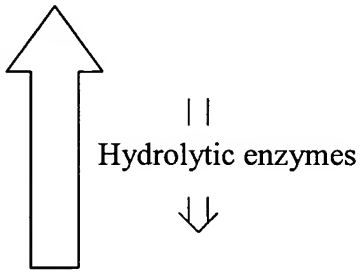


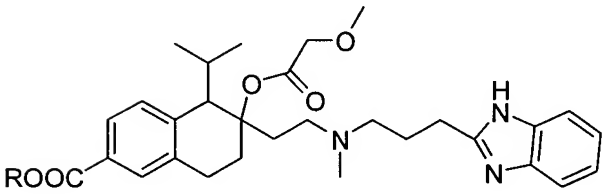
soft analog
R = lower alkyl optionally
substituted by OH or NH_2,
X is as defined above

Figure 3



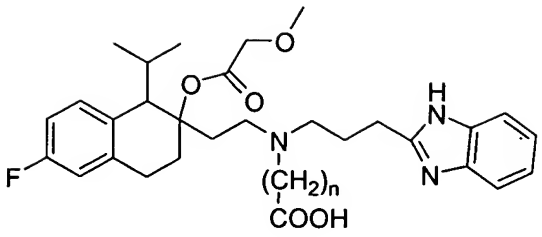
primary inactive metabolite



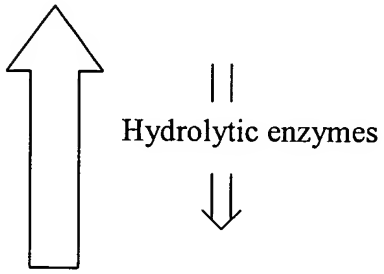


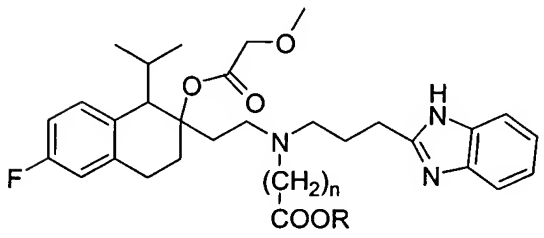
soft analog
R = lower alkyl optionally
substituted by OH or NH_2

Figure 4



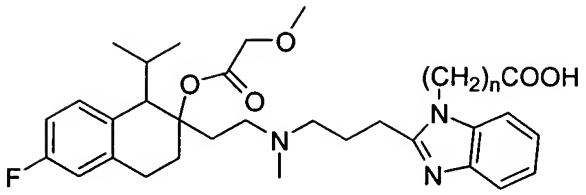
primary inactive metabolite
n = 1 to 3



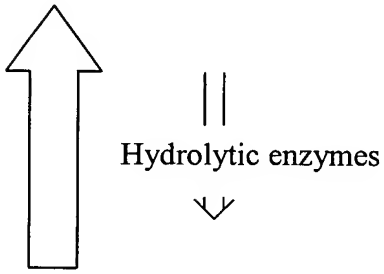


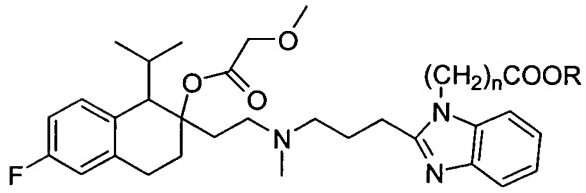
soft analog
n = 1 to 3
R = lower alkyl optionally
substituted by OH or NH_2

Figure 5



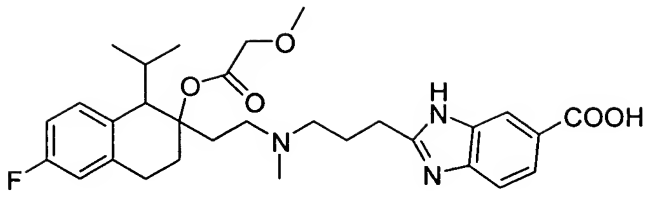
primary inactive metabolite
n = 1 to 3



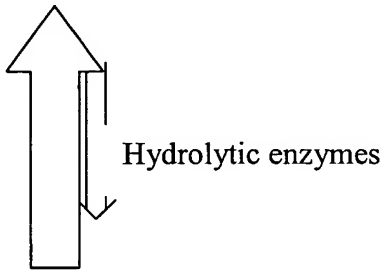


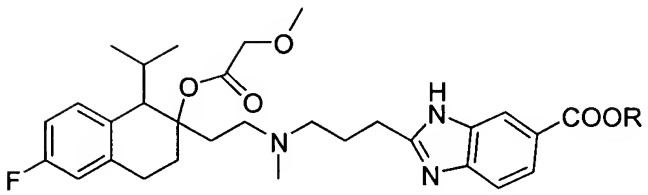
soft analog
n = 1 to 3
R = lower alkyl optionally
substituted by OH or NH_2

Figure 6



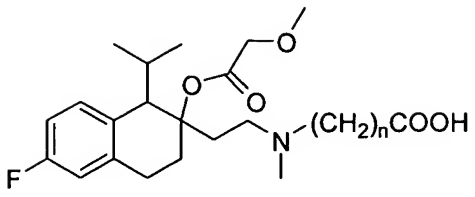
primary inactive metabolite



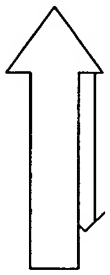


soft analog
R = lower alkyl optionally
substituted by OH or NH_2

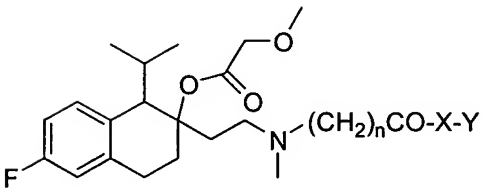
Figure 7



primary inactive metabolite
n = 1 to 3

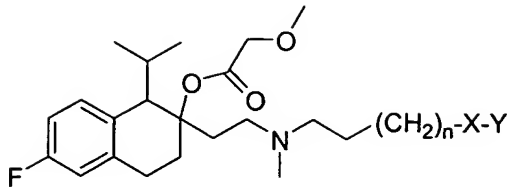


Hydrolytic enzymes

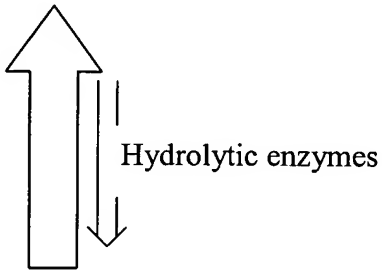


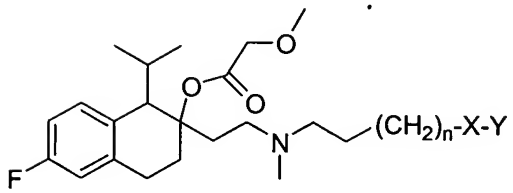
soft analog
n = 1 to 3
X = O, NH, NR where R
is lower alkyl
Y = optionally substituted aryl
or heterocyclyl

Figure 8



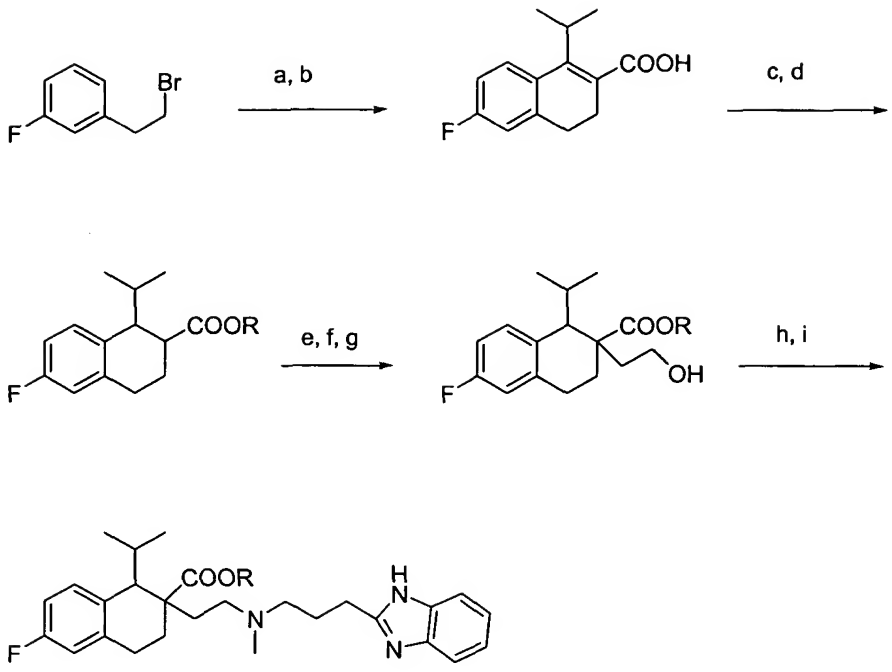
primary inactive metabolite
n = 0 to 2
X = O, S, SO, SO_2, NH, NR or $N(CH_2)_mCOOH$
where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$
where m is 0 to 2





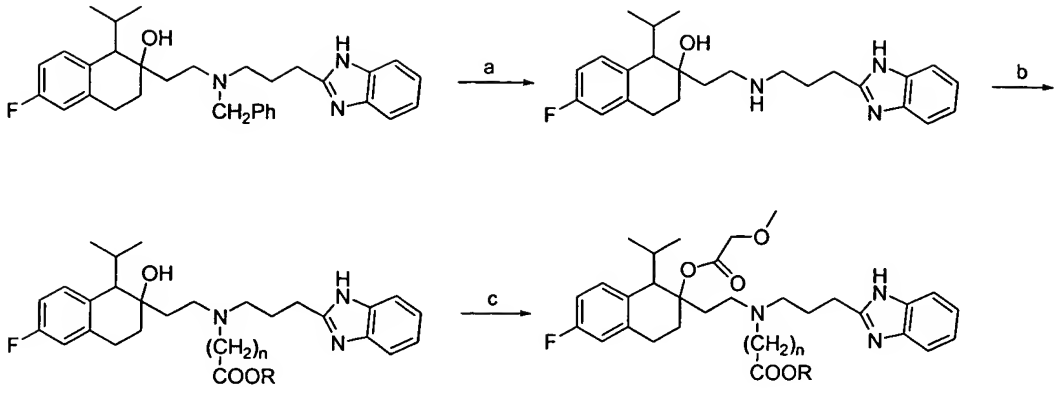
soft analog
n = 0 to 2
X = O, S, SO, SO_2, NH, NR or $N(CH_2)_mCOOR$
where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOR$
where m is 0 to 2
R = lower alkyl optionally substituted by OH or NH_2

Figure 9

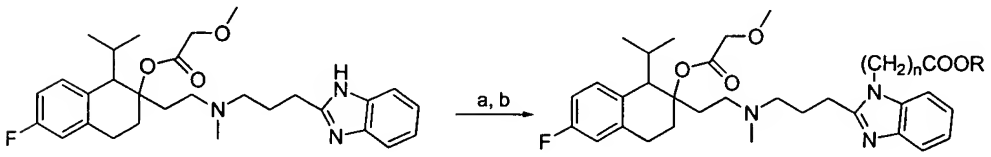


a, $iPrCOCH_2COOEt$, NaOEt; b, conc. H_2SO_4; c, ROH, H^+; d, H_2, Pd/C; e, LDA; f, $BrCH_2CH_2OTHP$; g, H^+; h, TsCl, TEA; i, 2-(N-methylaminopropyl)benzimidazole, K_2CO_3

Figure 10

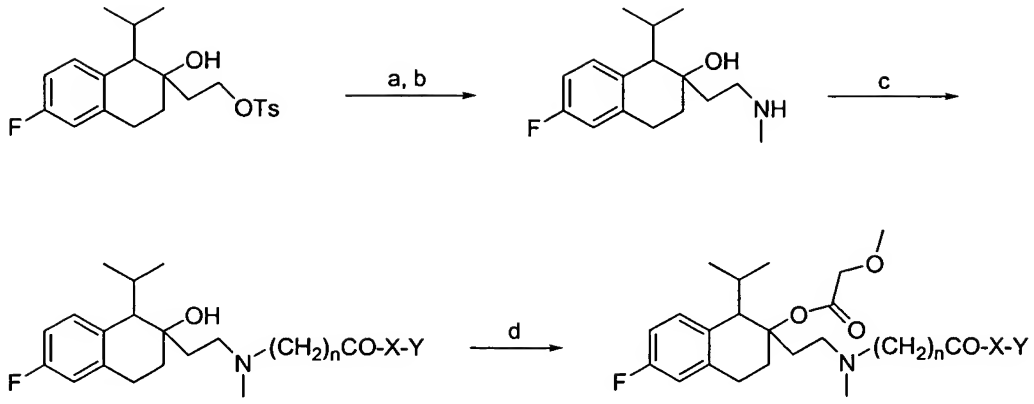


a, H_2, Pd/C; b, $Br(CH_2)_nCOOR$, K_2CO_3, DMF; c, $MeOCH_2COCl$, TEA, DMAP

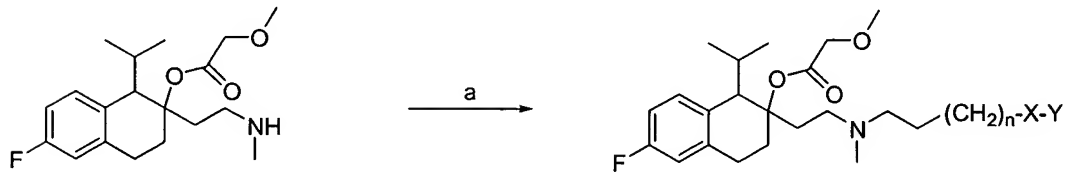


a, BuLi, THF; b, $Br(CH_2)_nCOOR$

Figure 11



a, N-methylbenzylamine, K_2CO_3; b, H_2, Pd/C, c, $Br(CH_2)_nCO$-X-Y, K_2CO_3; d, $MeOCH_2COCl$, TEA, DMAP



a, $BrCH_2CH_2(CH_2)_nCO$-X-Y, NaI, K_2CO_3, DMF

Figure 12